" ... the specification is enabled for OPG polypeptides that are unfused and consist of residues 22-401 of unfused human OPG and only unfused OPG of residues 22-194, 22-200, 22-201, 22-293 and 22-355 of mouse. Table 1 of WO 97/23614 teaches only these constructs result in bioactivity. In addition, the art of Simonet et al. ... teaches that loss of the C-terminal portion up to amino acid 194 did not affect activity (see page 315). Therefore the prior art teaches only specific OPG molecules are active and the claims still encompass any OPG of any residues as well as any truncated polypeptides of OPG. ... "

First, the Examiner's characterization of Table 1 of WO 97/23614 as set forth above is incorrect. Table 1 shows that the following OPG polypeptides have biological activity: murine OPG having residues 22-401-Fc, 22-194-Fc, 22-185-Fc, 22-401, 22-401(C195), 22-401(C202), 22-401(C319), 22-401(C400), 22-194, 22-200, 22-203, and 22-355; and human OPG having residues 22-401-Fc, 22-201-Fc, 22-401-Fc(P26A), 22-401-Fc(Y28F), 22-401, 27-401-Fc, 29-401-Fc, and 32-401-Fc. The results in Table 1 show many more active OPG polypeptides than alleged by the Examiner and, in particular, there are numerous examples of active fused OPG polypeptides as well as truncated OPG polypeptides.

Moreover, the Examiner has ignored other teachings in WO 97/23614 which point to additional OPG polypeptides which have activity, such as human OPG 22-194-Fc as shown in Example 12. In addition, the present applications discloses active OPG polypeptides having residues 22-194 or 22-201 fused to Fc molecules either at the amino-terminus or at the carboxy-terminus.

Taken together, the present application and WO97/23614 provides numerous examples of biologically active OPG polypeptides to support the scope of coverage being sought. Despite these examples, the Examiner characterizes the prior art (i.e, WO 97/23614 and Simonet et al.) as teaching that "only specific OPG molecules are active". Of course, "specific" molecules are tested for activity as representative examples of the types of biologially active OPG polypeptides . Based on these teachings, one skilled in the art would recognize that other OPG molecules not specifically tested may also have activity. For example, the disclosure that OPG polypeptides having residues 22-203 or 22-355 are both active suggests to one skilled in the art that OPG polypeptides of intermediate length are also likely to be active. Applicants should not be penalized for testing specific molecules by being limited to only those molecules.

It is requested that the rejection be withdrawn.

Claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for reciting a "mature OPG polypeptide". The Examiner argues that it is unclear how a mature OPG polypeptide is different from SEQ ID NO:2.

Applicants maintain that the term "mature OPG polypeptide" is clear to one skilled in the art. Moreover, the specification at p. 8, lines 7-10 states that " ... wherein full-length mature OPG has 380 amino acids, such as from residues 22-401 inclusive ... " It is maintained that the term "mature OPG polypeptide" is not indefinite.

Claims 42-53 and 56-58 are rejected under 35 U.S.C. 112, first paragraph, as it is alleged that the subject matter was not described in the specification in such a way as to convey possession of the claimed invention as of the time the application was filed. The Examiner argues that the phrase "a method for preventing abnormal bone formation associated with cancer" is not supported by the disclosure.

At p. 30, lines 32-36 of the specification, it is stated that "[t]he fusion polypeptides of the invention are used in the ... prevention and/or treatment of replacement of structurally sound bone with disorganized bone." Also, at p. 31, lines 25-29 is a reference to Paget's disease which is characterized by structurally abnormal bone. Applicants maintain that the subject matter of Claims 42-53 and 56-58 is adequately described.

Rejections under 35 U.S.C. 103

Claims 41-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyle et al. (PCT publication no. WO97/23614) in view of Conte et al. (Annals Oncol. 5 (Suppl. 7), S411-S44 (1994) and Simonet et al. (Cell 89, 309-319 (1997)). The Examiner argues that it would have been obvious to use an OPG polypeptide or an OPG fusion protein of Boyle et al. or Simonet et al. in the method of Conte et al. for the treatment of loss of bone mass associated with cancer. It is alleged that Conte et al. teaches treatment of breast cancer lytic metastasis with the combination of pamidronate and chemotherapy and it would have been obvious to interchange pamdironate and OPG because both molecules were known to inhibit loss of bone mass. Applicants disagree.

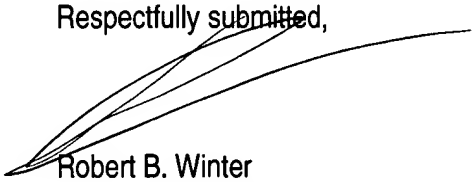
The rejection is clearly based on hindsight with knowledge of the invention. The Examiner is picking and choosing various parts of Boyle et al., Conte et al. and Simonet et al. to arrive at the claimed invention when there is no suggestion to one skilled in the art to do so. It is clear that the Conte et al. reference contemplated further trials with other bisphosphonates in combination with chemotherapy for

bone loss associated with cancer but did not in any way suggest that any anti-resorptive agent (whether or not it was a bisphoshponate) should be combined with chemotherapy to treat bone loss. The motivation to combine the references must be in the references themselves. The teachings of Conte are narrowly drawn to bisphosphonates and chemotherapy and there was no suggestion to substitute other classes of anti-resorptive agents. It is requested that the rejection be withdrawn.

CONCLUSION

Claims 41-58 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,



Robert B. Winter
Attorney/Agent for Applicant(s)
Registration No.: 34,458
Phone: (805) 447-2425
Date: August 7, 2003

Please send all future correspondence to:
U.S. Patent Operations/ RBW
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799